LISTING OF CLAIMS

1. (Previously presented) An anti-tumor drug and cobalamin conjugate comprising:
   a. cobalamin, or a derivative or analogue thereof;
   b. a linker covalently bound to the 5'-OH moiety of cobalamin or cobalamin derivative; and
   c. an anti-tumor drug covalently bound to the linker thereby forming the conjugate wherein the drug is cleavable from the linker and/or the linker is cleavable from the drug by an intracellular enzyme; the conjugate is adapted for transport across a cellular membrane after complexation with transcobalamin; the drug is cleavable from the linker and/or the linker is cleavable from the drug by an intracellular enzyme; and the conjugate optionally possesses one or more protecting groups.

2. (Original) The anti-tumor drug and cobalamin conjugate of claim 1, wherein cobalamin is selected from the group consisting of vitamin B12, cyanocobalamin, aquocobalamin, hydroxycobalamin, methylcobalamin, adenosylcobalamin, cyanocobalamin carbanalide, desdimethyl cobalamin, monoethylamide cobalamin, methlyamide cobalamin, coenzyme B12, 5'-deoxyadenosylcobalamin, cobamamide derivatives, chlorocobalamin, sulfitocobalamin, nitrocobalamin, thiocyanatocobalamin, benzimidazole derivatives such as 5,6-dichlorobenzimidazole, 5-hydroxybenzimidazole, trimethylbenzimidazole, as well as adenosylcyanocobalamin ((Ade)CN-Cbl), cobalamin lactone, cobalamin lactam and the anilide, ethylamide, monocarboxylic, dicarboxylic and tricarboxylic acid derivative of VB12, proprionamide derivatives of VB12, 5-o-methylbenzylcobalmin, and analogues thereof wherein the cobalt is replaced by another metal.

3. (Original) The anti-tumor drug and cobalamin conjugate of claim 1, wherein the anti-tumor drug is selected from the group consisting of doxorubicin and taxol.

4. (Original) The anti-tumor drug and cobalamin conjugate of claim 1, wherein the linker is cleavable by way of an intracellular enzyme selected from the group of enzyme classes consisting of cathepsin, endo enzyme, glycosidase, metalloprotease, ribozyme, protease, esterase, and amidase.

5. (Original) The anti-tumor drug and cobalamin conjugate of claim 1, wherein the conjugate possesses reduced systemic toxicity as compared to the corresponding free anti-tumor drug.

6. (Original) A method of treating a tumor related disorder or disease comprising the step of administering to a subject in need thereof a therapeutically effective amount of conjugate according to claim 1.

7. (Previously presented) An anti-tumor drug and cobalamin conjugate of the formula I:

$$VB\text{-}(SPa)_n\text{-}CL\text{-}(SPb)_m\text{-}DG$$

Formula I

wherein,

a. CL is a linker that is cleavable from the VB, SPa, SPb and/or DG by way of intracellular enzyme;

b. VB is cobalamin, or a derivative or analogue thereof, covalently bound to CL and SPa, if present, via the 5'-OH group of the ribose ring of VB;

c. SPa and SPb are optional spacers independently selected at each occurrence from the group consisting of a covalent bond, divalent functional group, or non-peptide residue, wherein SPa and SPb can be located on either side of CL; and

d. DG is an anti-tumor drug possessing one or more functional groups by way which it is covalently bound to a spacer or CL; wherein n and m

are independently selected at each occurrence from 0, 1, or 2; and the conjugate optionally possesses one or more protecting groups.

8. (Previously presented) The anti-tumor drug and cobalamin conjugate of claim 7, wherein the divalent functional group is selected from the group consisting of -NHNH-, -NH-, -O-, -S-, -SS-, $-CH_2-$, -NHCO-, -CONH-, -CONHNHCO-, -N=N-, -N=CH-, $-NHCH_2-$, -NHN=CH-, $-NHNHCH_2-$, $-SCH_2-$, $-CH_2S-$, -NHC=ONH-, -NHC=SNH-, -NHC=NHNH-, -COO-, and -OCO-.

9. (Previously presented) The anti-tumor drug and cobalamin conjugate of claim 7, wherein cobalamin is selected from the group consisting of vitamin B12, cyanocobalamin, aquocobalamin, hydroxycobalamin, methylcobalamin, adenosylcobalamin, cyanocobalamin carbanalide, desdimethyl cobalamin, monoethylamide cobalamin, methylamide cobalamin, coenzyme B12, 5'-deoxyadenosylcobalamin, cobamamide derivatives, chlorocobalamin, sulfitocobalamin, nitrocobalamin, thiocyanatocobalamin, benzimidazole derivatives, 5,6-dichlorobenzimidazole, 5-hydroxybenzimidazole, trimethylbanzimidazole, adenosylcyanocobalamin ((Ade)CN-Cbl), cobalamin lactone, cobalamin lactam and the anilide, ethylamide, monocarboxylic, dicarboxylic and tricarboxylic acid derivatives of VB12, proprionamide derivatives of VB12, 5-o-methylbenzylcobalmin, and analogues thereof wherein the cobalt is replaced by another metal.

10. (Original) the anti-tumor drug and cobalamin conjugate of claim 7, wherein n and m are independently selected from 1, 2 or 3.

11. (Original) The anti-tumor drug and cobalamin conjugate of claim 7, wherein the non-peptide residue is selected from the group consisting of $-NH-C_6H_4-CH_2-O-$ and $-NH(CH_2)_5C(=O)-$.

12. (Original) The anti-tumor drug and cobalamin conjugate of claim 7, wherein the anti-tumor drug is selected from the group consisting of doxorubicin and taxol.

13. (Previously presented) The anti-tumor drug and cobalamin conjugate of claim 7 having the one of the following formulas:

a. VB-$(SPa)_p$-CL-DG (Formula II);

b. VB-CL-$(SPb)_q$-DG (Formula III);

c. VB-CL-DG (Formula IV);

d. VB-CL-$(SPa)_p$-$(SPb)_q$-DG (Formula V);

e. VB-$(SPa)_p$-$(SPb)_q$-CL-DG (Formula VI);

f. VB-$(SPa)^2(SPa)^1$-CL-$(SPb)^2$-DG (Formula VII);

wherein p and q are independently selected from 1, 2 and 3.

14. (Original) The anti-tumor drug and cobalamin conjugate of claim 13 wherein:

a. $(SPa)^1$ and $(SPb)^1$ are each independently selected at each occurrence from a divalent functional group and a covalent bond; and

b. $(SPa)^2$ and $(SPb)^2$ are each independently selected at each occurrence from a non-peptide residue.

15. (Original) The anti-tumor drug and cobalamin conjugate of claim 14, wherein:

a. $(SPa)^2$ and $(SPb)^2$ area each a divalent carbonyl; and

b. $(SPa)^2$ and $(SPb)^1$ are each an –NH-, -S-, and/or -O- containing non-peptide residue.

16. (Original) The anti-tumor drug and cobalamin conjugate of claim 7, wherein the linker is cleavable by way of an intracellular enzyme selected from the group of enzyme classes consisting of cathepsin, endo enzyme, glycosidase, metalloprotease, ribozyme, protease, esterase, and amidase.

17. (Original) The anti-tumor drug and cobalamin conjugate of claim 7, wherein the conjugate possesses reduced systemic toxicity as compared to the corresponding free anti-tumor drug.

18. (Original) The anti-tumor drug and cobalamin conjugate of claim 17, wherein the conjugate possesses improved efficacy on a molar basis than the corresponding free anti-tumor drug.

19. (Original) the anti-tumor drug and cobalamin conjugate of claim 7, wherein the one or more functional groups are selected from the group consisting of a primary or secondary amine, hydroxyl, sulfhydryl, carboxyl, hydrazide, nitrile, aldehyde, and ketone.

20. (Original) The anti-tumor drug and cobalamin conjugate of claim 7, wherein the one or more functional groups comprises a derivatizable site on DG.

21. (Original) A method of treating a tumor related disorder or disease comprising the step of administering to a subject in need thereof a therapeutically effective amount of a conjugate according to claim 7.